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13. ABSTRACT *(Maximum 200 Words)*

This is the final report for a research project supporting the development of a technique for breast cancer treatment using ultrasound hyperthermia as an adjuvant to standard treatment using radiation. A breast treatment applicator and associated instrumentation has been completed and tested. The applicator consists of 384 ultrasound transducers in a cylindrical geometry, specifically designed for hyperthermia of the intact breast. The results of the acceptance testing are presented in this progress report. The breast treatment system allows hyperthermia of a quadrant of the breast, half the breast or the whole breast. The device was originally designed for the treatment of early stage breast cancer (Ductal Carcinoma in Situ, DCIS and Extensive Intraductal Carcinoma, EIS). A protocol for a device evaluation study on patients with this disease was developed. However, the treatment options of this disease have changed in the course of the technical developments and today, the standard treatment for women with extensive DCIS is mastectomy. Therefore, as written the protocol has not been able to accrue any patients. A new protocol is being prepared for future us of the breast therapy system. New funding will be sought for this new protocol.

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Gorm Svensa 9/30/99

PI - Signature Date

III. Table of Contents:

Page number.

IV. Introduction.

1. Clinical problem, background and hypothesis:

Thermal Therapy or Hyperthermia (sustained tissue temperature at 40.5°C - 44°C) adjuvant to radiation has been shown in the laboratory to increase cell killing (1 - 17). Clinical investigations show that the combination of hyperthermia with radiation therapy or with cytotoxic agents improve the complete response rate of many cancers (18 - 20). A large European randomized study with over 300 patients with recurrent or primary inoperable breast cancer showed an overall complete response rate of 60 % when using radiation plus hyperthermia as compared to 40 % for radiation alone (21). The investigators in that study emphasize that current general purposes hyperthermia treatment devices may be inadequate for the treatment of relatively deep tumors in intact breast. Novel and optimized technology that allows reaching hyperthermic temperatures to the whole breast or to any tumor bearing volume in the breast is thus essential to reach adequate thermal dose and meet the goals of this proposal. We wish to accomplish hyperthermia treatment of the breast by using a multi-frequency high-resolution site-specific ultrasound applicator.

Contract DAMD 17-93-C-3098 has supported the development of a technique for adjuvant treatment of breast cancer using hyperthermia generated by a site-specific ultrasound device. Ultrasound is capable of penetrating soft tissues to produce deep heating. The research also intended to support a clinical study of the safety and efficacy of using hyperthermia in combination with radiation for treatment of breast cancer patients with an extensive intraductal component of their infiltrating tumor or patients with pure intraductal carcinoma. Breast cancer patients with these histologies have a higher risk of local recurrence after treatment with radiation alone than patients without these histologies (22 - 32).

Intraductal carcinoma is characterized by cancer cells spreading within the lactiferous ducts. It is suggested that intraductal carcinoma is associated with tumor necrosis within the ducts and that the necrotic tumor cells are related to the absence of blood supply with resulting hypoxia (26). It is well known that thermal therapy, in contrast to radiation, is more effective in killing hypoxic cells as compared to well-oxygenated cells (33, 34, 35).

At the time of the grant submission in 1992, the clinical rationale and hypothesis for this work was that patients with infiltrating breast cancer containing an extensive intraductal component or patients with pure intraductal carcinoma will have a reduced risk for local recurrence from a combined and non-disfiguring treatment approach using hyperthermia and irradiation. It was postulated that these conditions would extend the indications for breast conserving therapy and eliminate the need for mastectomy for many patients. It was also assumed that there may be a population of patients with early stage breast cancer, where the hyperthermia treatment can replace radiation treatments and eliminate radiation associated toxicities to normal tissues in the treated breast, in the opposite breast, and toxicities to heart and lungs.

The protocol for the treatment of DCIS disease was written and submitted to the Dana Farber Cancer Institute Internal Review Board in 1996. It was subsequently approved by the FDA and by the US Army Human Use Review and Regulatory Affairs Division. However, since that time, the field of breast cancer diagnosis and therapy has moved forward and today there is a different approach to the treatment of this disease. The current approach by the physician groups at DFCI is that women with extensive DCIS throughout the breast are best treated with a mastectomy. Therefore, as written, the Protocol has not been able to accrue any patients.

After much discussion with Irving Kaplan, M.D. PI for the clinical protocol, and colleagues at the Joint Center for Radiation Therapy (JCRT), it was decided to rewrite the protocol with new inclusion criteria. Specifically, the new protocol will include patients with focal or close margins (within 2mm). This is especially attractive for women who present with larger DCIS lesions that are completely excised or women with comedo necrosis, both of which have been suggested to be negative prognostic factors for breast conservation. However, this new protocol needs to be approved by the local hospital IRB, and the US Army Human Use Review and Regulatory Affairs Division in addition to a new Investigational Device Exemption from the FDA, a process that by itself will take approximately 9 months. A new cost extension to this contract will therefore have to be approximately 15 months to assure enough time for protocol approvals, a new IDE and a reasonable patient accrual. It is not possible for the remaining clinical funds to support such an effort, and our approach will be to seek additional funding for the clinical testing and use of the breast hyperthermia device designed and constructed under this Army contract.

Our research postulates that hyperthermia is most effectively and controllably delivered to the breast tissue using a breast site specific ultrasound applicator. During year 01 and 02 (April 1, 1993 to March 31 1995), the breast treatment applicator and the associated complex instrumentation system was designed, fabricated and tested. This has been described in detail in previous Annual Progress Reports. The third contract year began on April 1, 1995. Due to unforeseen technical, scientific, and regulatory problems, this research has taken significantly more time than originally anticipated. As a result, I have requested and received a No-Cost extension of this program on three occasions, first from April 1, 1996 to December 31 1996 and the second time from January 1, 1997 to May 31, 1998, and the third time from June 1, 1998 to August 31, 1999. In spite of a delay in progress, the quality of the treatment system is excellent. The technical hypothesis and goals of this program remain the same. However, as discussed above, the treatment of DCIS breast cancer has drastically changed necessitating a new treatment protocol.

The technical rationale and criteria for the design of the ultrasound therapy system and applicator are derived from the tissue characteristics and features of the breast:

a. The breast is an external, convex shaped organ. When submerged into a temperature controlled water bath, the temperature boundaries are well defined and the skin temperature can be well controlled.

b. Ultrasound heating is suitable for the breast, because there is no intervening gas or bone in the breast tissue. With the patient in prone position and the breast submerged into a water bath, the breast tissue can be surrounded with an array of ultrasound transducers and achieve tangential incidence of the ultrasound beam relative to the chest wall. Tangential incidence is desired to avoid interaction between the ribcage and the ultrasound pressure wave.

c. There are no major blood vessels that carry away heat from the breast tissue, which can reduce the ability to deliver therapeutic heat.

d. The hyperthermia target volume can be the whole breast, a quadrant of the breast, or even a smaller specific tumor mass. Energy deposition, which may heat sensitive regions, such as a lumpectomy scar must be avoided or minimized. It is therefore essential that the energy deposition be controlled and focused on specific sites within the breast tissue. Ultrasound permits this level of control.

e. Although our initial pilot study will aim for a target temperature of $T_{90} > 40.5^{\circ}C$ (T_{90} means the temperature reached by 90% of the sensors) and $T_{max} < 45^{\circ}C$, the device must be able to heat the breast tissue within an even more narrow temperature range ($42^{\circ}C$ - $44^{\circ}C$) over a reasonable range of tissue perfusion (i.e. 30 to 200 ml, kg^{-1}, min^{-1}).

2. Specific Research Objectives.

The first research objective was to build a cylindrical, multi-transducer, dual frequency, intensity controlled ultrasound therapy system and applicator for treatment of breast cancer. The device must be capable of delivering controllable energy for the purpose of heating the whole breast or a small volume of breast tissue as defined by the clinical situation and the criteria in section V.2.A. The intensity control of the applicator must permit heating within a narrow temperature range, i.e. $42^{\circ}C < T_{tissue} < 44^{\circ}C$. Many scientific and technical problems associated with the individual subsystems have now been solved and the sophisticated system has been assembled in the laboratories at the Dornier Medical Systems, Inc., Champaign, Illinois.

A second objective was to develop an effective pre-treatment planning and real-time treatment control system. One aspect of this effort is to perform the thermal therapy using dense thermometry. It is essential for the assessment of outcome that temperatures are measured during thermal therapy in a large number of points throughout the breast tissue volume. The objective is to accomplish this through new technologies using minimally invasive or non-invasive thermometry. The minimally invasive temperature measurements has been achieved by using small multi-sensor thermistor probes (dense thermometry), developed at the Massachusetts Institute for Technology (MIT) under the direction of Dr. F. Bowman, who is a consultant to our contract (36). To augment the dense thermometry mapping, we have implemented a technique for real time imaging of the breast surface. This is important for monitoring of the location of the breast tissue within the treatment cavity and thus for control of power deposition in the breast.

A third objective was to develop an ultrasound thermal therapy protocol. A protocol was developed for treatment of women, who presented with extensive ductal carcinoma in situ (DCIS). This protocol has not been able to accrue any patients, and new protocols with different inclusion criteria will be needed for the future.

V. BODY OF ANNUAL REPORT

1. Program Organization.

This contract was originally sponsored by the New England Deaconess Hospital (NEDH); a Harvard Medical School (HMS) affiliated hospital in Boston, Massachusetts. In 1996, the NEDH and another HMS affiliated hospital, the Beth Israel Hospital merged into one institution with the name Beth Israel Deaconess Medical Center (BIDMC). BIDMC is now the sponsor of this contract. The program director, Goran K. Svensson, Ph.D. is an Associate Professor at HMS and he is responsible for the progress of the scientific, technical and clinical developments. Dr. Svensson is also the Director of Physics at the Joint Center for Radiation Therapy (JCRT). Irving Kaplan, M.D. is the PI for the clinical protocol(s). The JCRT provide radiation therapy and thermal therapy (hyperthermia) services for patients from the BIDMC, the Dana Farber Cancer Institute (DFCI), Brigham and Women's Hospital (BWH) and Children's Hospital (CH). These hospitals are all affiliated with Harvard Medical School.

In addition the JCRT provides service to several community hospitals in Boston and the South Eastern part of Massachusetts. An important aspect of this program is that this treatment technology will be available to women in the outreach community where academic medicine is not normally available.

All clinical work will be done at the BIDMC and at DFCI. Clinical research protocols used by the JCRT member hospital network require IRB approval from the participating hospitals. The DFCI has a large Breast Evaluation Center (BEC), which is an important referral base for breast cancer patients. We have therefore chosen to seek IRB approval for hyperthermia, using this device, from DFCI and from the sponsoring hospital BIDMC.

Theoretical simulations and treatment planning require large computational resources. This work took place at the BIDMC or DFCI using a distributed computer network with a centrally located 60 Gigabyte server.

The electronic design and the fabrication of the ultrasound treatment system and breast applicator was subcontracted to Dornier Medical Systems Inc. (DMSI) with headquarters in Atlanta, Georgia. The actual work has been performed at the DMSI R&D Laboratory in Champaign, Illinois under the direction of Everette C. Burdette, Ph.D. Dr. Burdette directed advanced technology research for DMSI. The breast treatment system has been completed, and is currently in place at its clinical site in Boston.

2. Summary of Progress to August 31st, 1999.

A. Introduction.

The clinical rationale and hypothesis for this work has been that patients with infiltrating breast cancer containing an extensive intraductal component or patients with pure intraductal carcinoma will have a reduced risk for local recurrence from a combined and non-disfiguring treatment approach using hyperthermia and irradiation. This would have extended the indications for breast conserving therapy and eliminate the need for mastectomy for many patients. However, due to the different approach the last few years to treat DCIS breast cancer, this hypothesis is no longer valid and new protocols are under development that will benefit from the technology developed under this contract. However, the technical treatment issues associated with the new inclusion criteria are identical to the ones that existed under the old protocol. Thus the hyperthermia treatment associated with the new inclusion criteria will be most effectively and controllably delivered to the breast tissue using a site-specific ultrasound Breast Therapy System (BTS).

Toxicities associated with hyperthermia are well documented (12, 13, 37). One major concern addressed in the design of the system is that women that have undergone lumpectomy or surgical biopsy are left with a scar cavity within the breast. Scar tissue, in general, has much lower perfusion than surrounding normal tissue. Clinical experience has revealed that the poorly perfused scar tissue can easily over-heat during hyperthermia that can cause a burn or a blister as an undesired toxicity. The BTS must have very accurate temporal and spatial power control to reduce the temperature in and around the scar tissue. To achieve this level of control and spatial resolution, 384, 1.5x1.5 cm^2 square transducers are incorporated in the cylindrical site-specific applicator. The control of these ultrasound therapy transducers is augmented by minimally invasive thermometry and non-invasive monitoring. The power level to each transducer is independently controlled.

The technical rationale and criteria for the design of the ultrasound therapy system and applicator are derived from the tissue characteristics and features of the breast. These criteria are unchanged and they are described in the Introduction on page 6 - 7.

B. Completion of the hyperthermia Breast Treatment System (BTS).

To reach the clinical goal, defined in section IV, we have designed, built, and tested a Breast Therapy System (BTS), which now is ready for clinical use. The system was fully described in the 1997 annual report, but a brief summary is given here. Figure 1 shows the completed BTS.

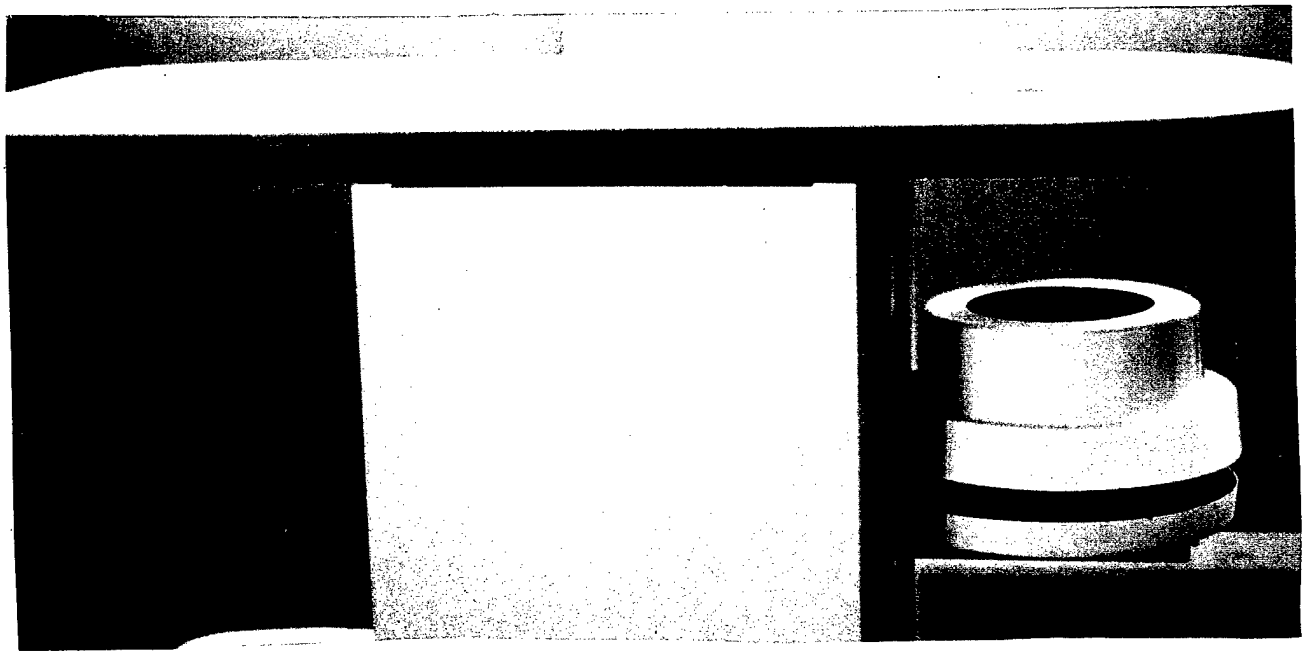


Figure 1. Completed BTS. All electronics and control computers are mounted in the center column of the machine.

The BTS consists of several subsystems. The major subsystems and their relationships are shown schematically in Figure 2.

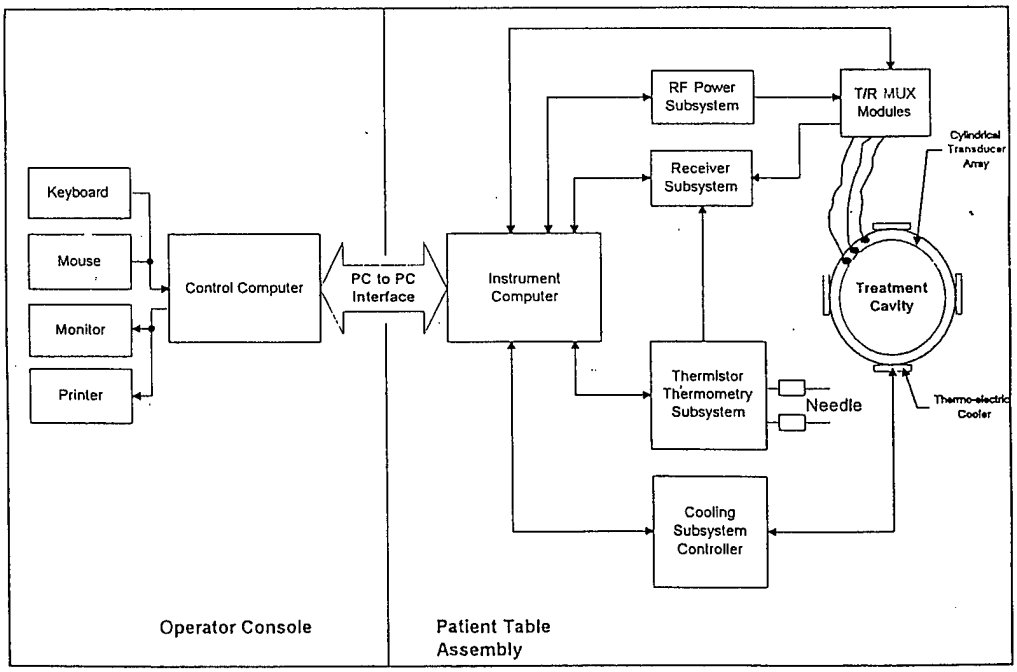


Figure 2. Schematic drawing of the BTS subsystems.

The individual systems are briefly described below using the terminology from Figure 2.

1. The ultrasound breast applicator consists of the cylindrical transducer array and the treatment cavity. The cylindrical transducer array surrounds the breast, which is submerged into the treatment cavity. The applicator is schematically illustrated in Figure 3 and a photograph of the completed applicator on the table frame is shown in Figure 4. The array consists of eight individual rings, which are stacked with watertight seals between each ring. Each ring accommodates 48 transducers. Each transducer has a square emitting face with dimensions of 1.5 cmx1.5 cm. Computer simulations (41 - 43) show that three different frequencies are needed to achieve sufficient control of the heating pattern. Table 1 shows the number of rings, transducers per ring and the frequencies of the transducers in each ring. Table 2 shows the expected ring activation for the treatment of a large breast and a small breast. Each transducer was fabricated with the crystal mounted in a machined transducer housing, sealed watertight and faced with a matching layer. Each transducer was individually tested to determine operating acoustic efficiency, center frequency and bandwidth. More details are available in the 1997 annual report.

Cylindrical Transducer Array

Number of XDucers	Ring Number
48	1
48	2
48	3
48	4
48	5
48	6
48	7
48	8

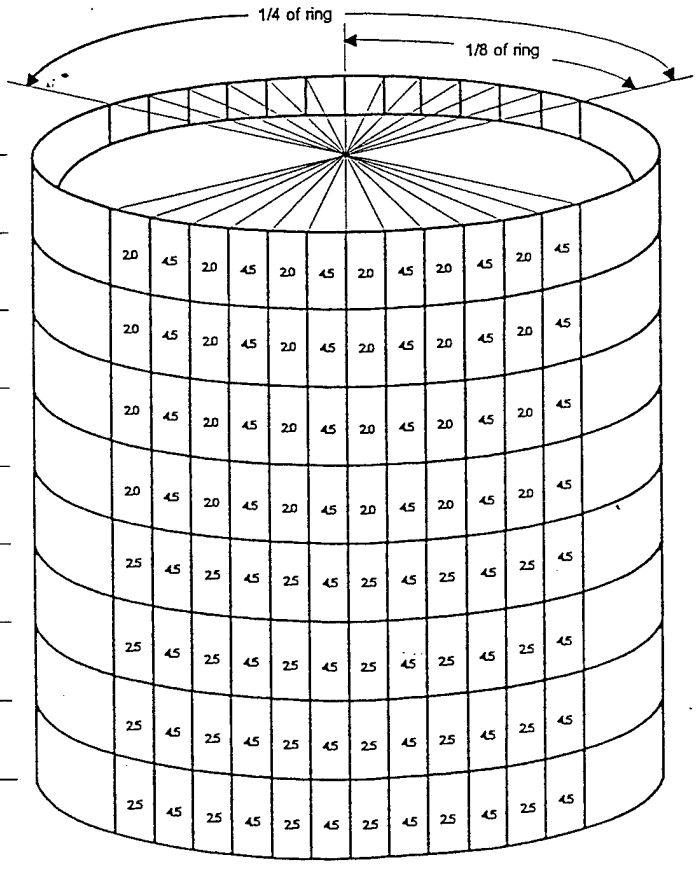


Figure 3. Applicator shown schematically.

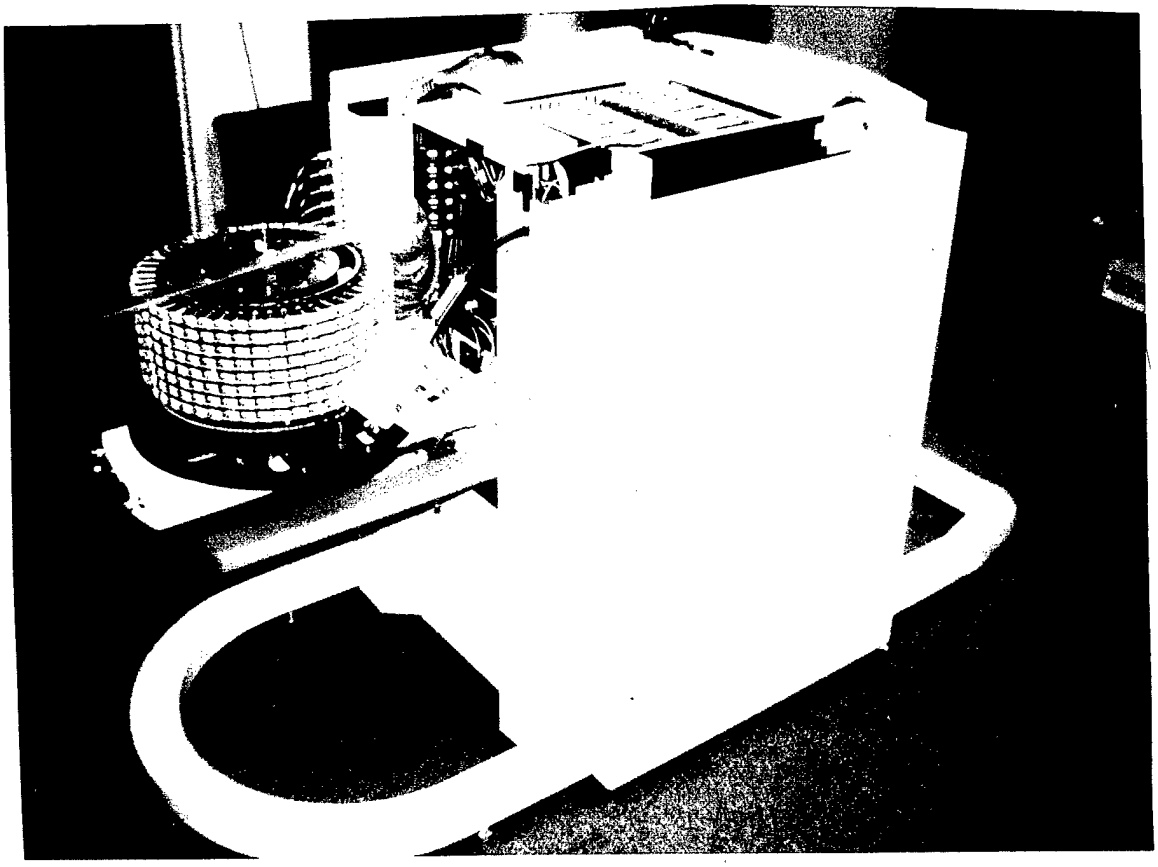


Figure 4. Completed applicator transducer array mounted on table frame. The Agar-Graphite breast phantom is submerged into the treatment cavity. Also see figure 5.

	Total Cylinder I.D. = 25 cm Transducers: 15 mm x 15 mm Rings of Transducers: 10 (numbered from top down) Each 1/8 ring vertical section driven by RF Amplifiers whose outputs are multiplexed to step around ring		
Ring No.	FQ 1 (MHz)/No. XDCRS	FQ 2 (MHz)/No. XDCRS	TOTAL XDCRS
1	4.5/24	2.0/24	48
2	4.5/24	2.0/24	48
3	4.5/24	2.0/24	48
4	4.5/24	2.0/24	48
5	4.5/24	2.5/24	48
6	4.5/24	2.5/24	48
7	4.5/24	2.5/24	48
8	4.5/24	2.5/24	48
		TOTAL	384

Table I. Description of transducers and frequencies in each ring.

Total Cylinder I.D. = 25 cm Transducers: 15 mm x 15 mm Rings of Transducers: 8 (numbered from top down) Each 1/8 ring vertical section driven by RF amplifiers whose outputs are multiplexed to "step around" ring				
Ring No.	No. Transducers	Breast Size (cm) Large	Small	No Transducers in 1/8 of ring
1	48	15	8	6
2	48	14	7	6
3	48	12	6	6
4	48	10	5	6
5	48	8	4	6
6	48	7	3	6
7	48	6	0	6
8	48	4	0	6

Table 2. Illustration of how many rings and transducer elements in each ring that will be activated when treating a large breast and a small breast respectively.

2. Systems control is performed by a control computer and an instrument computer. When power is turned on to the system, the treatment software initializes automatically so that no interaction is required by the user to start the software. All available options are displayed on the start-up screen, including access to treatment planning software, file handling utilities, diagnostic mode selection, treatment record printing and treatment initiation.

   Prior to the beginning of a treatment, the user will be required to complete a treatment plan. The treatment planning software is in graphical form to simplify data entry such as target volume outline, the number and locations of temperature sensors, temperature and thermal dose for each sensor, scar tissue location and patient information. Since the external contour of the breast is monitored in real time prior to and during treatment, the breast contour(s) with sensor location, scar tissue location and thermal dose information is displayed on an operator's screen. Guided by this information, the operator may manually select and control the power on any transducer or group of transducers (e.g. reduce power deposition directly over the scar).

   Temperatures and thermal dose are determined in two ways. The thermistor thermometry subsystem supports the use of multisensor (14 sensors) temperature probes that are placed in the breast tissue following guidelines from the Radiation Therapy Oncology Group (RTOG) (39 - 40). The thermometry subsystem provides real time temperature information and real time thermal dose data (i.e. $CEMT_{10}$,

which stands for the Cumulative Equivalent Minutes for 10% of the sensors reaching 43°C).

3. The RF power subsystem, the receiver subsystem, and the cooling subsystem controller are important electronic modules of the system. A description of these systems is available in the Systems Description Manual, which was appended to the 1997 annual report.

4. The patient table assembly is shown in Figures 1. The patient table is designed similar to a stereotactic breast biopsy table, allowing the breast to be suspended through an opening in the tabletop. The tabletop consists of sheet steel with a tubular steel outer frame fabricated to provide for insertion of a 1.5" foam padding.

   The central column or "pedestal" beneath the table houses all of the system electronics (Figure 4), and the appearance of the total system is clean, appealing, and without any clutter of cables and instruments.

5. Experimental studies have been performed throughout the whole development phase of the BTS. The studies have demonstrated that the BTS can deliver a power deposition capable of achieving uniform temperatures within 2°C. This is achieved by using individual amplifier power control and three ultrasound transducer frequencies; 2.0 MHz, 2.5 MHz and 4.5 MHz. The range of power control is expected to be greater than the clinical requirements. Consequently, it will be possible to adequately treat a wide variety of clinical situations and over a large range of breast tissue parameters, such as various perfusion and temperature boundary conditions. These studies also demonstrated the system's ability to control power deposition in each octant, quadrant, half and whole volume of the breast. The experiments also demonstrated deep and shallow heating control and individual transducer control. Our experiments did not show any unpredictable hot or cold area (41). This demonstrates that there are no constructive or destructive interferences between the ultrasound transducers that would create hot or cold areas. We have therefore concluded that the electronic design and the multiplexer switching arrangements have been successfully implemented.

C. Acceptance testing of BTS.

Experimental methods:

The hardware and software modules of the BTS were assembled and ready for acceptance testing in February/March 1996. The research team from the JCRT-BIDMC traveled to Champaign, Illinois, where the BTS has been designed and manufactured. The team spent a total of eight days carefully analyzing the system with respect to its ability to safely deliver hyperthermia to breast phantoms. A large number of measurements were performed and later analyzed. However, the system was not accepted by the research team during the February/March visit. There were significant problems with the control algorithm which prevented adequate control of the power deposition, and caused software crashes of the system. The software problems were fixed during the summer of 1996 and the team returned for testing in August of 1996, at which time the system was accepted.

In order to increase the density of temperature sensors available for dense thermometry and mapping of thermal dose distributions, a 32-channel thermometry system was brought from BIDMC supplementing the 84 channel thermometry system built into the BTS.

The BTS was tested using non-perfused phantoms designed to mimic the physical shape and ultrasound properties of the intact female breast. The phantoms were constructed from a latex membrane, shaped like an average breast, filled with an Agar-graphite-alcohol mixture formulated to yield a velocity of sound of 1540 m/sec and an absorption coefficient of 0.75 dB/cm both at 1 MHz. The phantom mixture, which is prepared hot, solidifies after being filled into the latex membrane and being allowed to cool down.

The phantom experiments were primarily designed to test the basic design philosophy of the BTS. The hyperthermia applicator was constructed with half the transducers operating at a low frequency of 2.0 to 2.5 MHz and the other half at a high frequency of 4.5 MHz. The low frequency transducers were designed to deposit energy at the core of the breast, and the high frequency transducers to deposit power at the treatment volume boundaries thereby compensating for thermal conduction to the non-heated surroundings of the breast. During patient treatments, all transducers will be activated initially in order to raise the temperature in all of the target area. When the core of the target area reaches therapeutic levels, the power to the low frequency transducers will be decreased thus lowering the power delivered to the core of the target area. During the remainder of the treatment the power delivered to the high frequency transducers will be controlled to compensate for thermal conduction from the surface of the breast to the coupling water and maintaining therapeutic temperatures in the surface of the breast.

The tests were also designed to test ability of the BTS to treat any part of the breast including any quadrant of the breast, any half of the breast, or the whole breast.

Correlation between power deposition fields and temperature fields are dependent upon the exact perfusion (or blood flow) patterns in the breast. Due to the non-perfused nature of the phantom, the main emphasis of these experiments was placed on measuring power deposition field in the phantoms. In hyperthermia, power deposition is commonly measured as Specific Absorption Rate (SAR) with the unit J/kg,sec. If temperature measurements are performed immediately after a power field has been imposed on the phantom, and before any significant temperature gradient has build up, then SAR = $c/\rho * dT/dt$., where c is the specific heat capacity and ρ is the specific density of the phantom material. Both these factors are physical constants of the phantom material, which leaves SAR proportional to the rate of temperature rise dT/dt measured in units of ^{O}C per unit time.

During experiments the phantoms were heavily instrumented with temperature probes containing up to 14 temperature sensors each. Up to 5 probes, each with 14 temperature sensors, were carefully implanted in the phantoms for each experiment and their exact position in the phantom determined. Figure 5 shows a photograph of the phantom and the temperature probes.

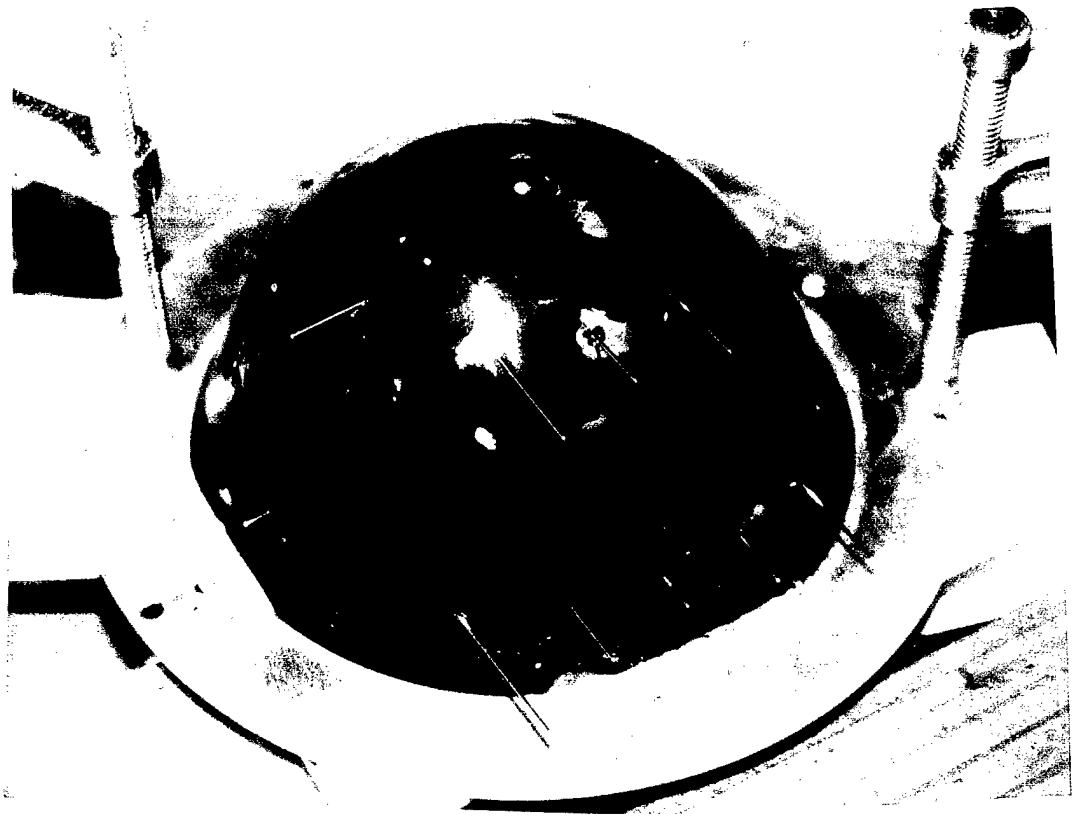
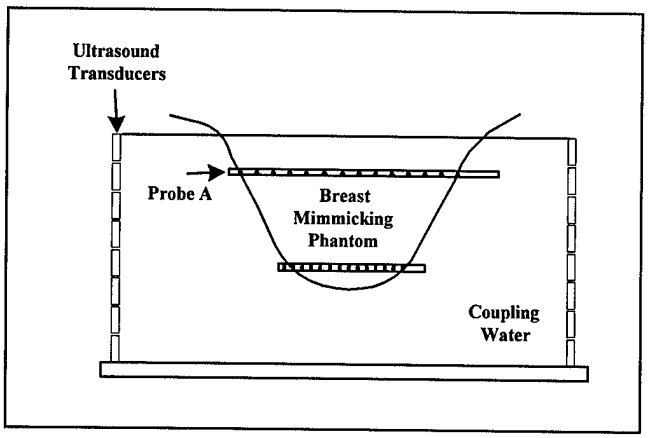


Figure 5. Agar-Graphite phantom with array of 14 sensor probes.



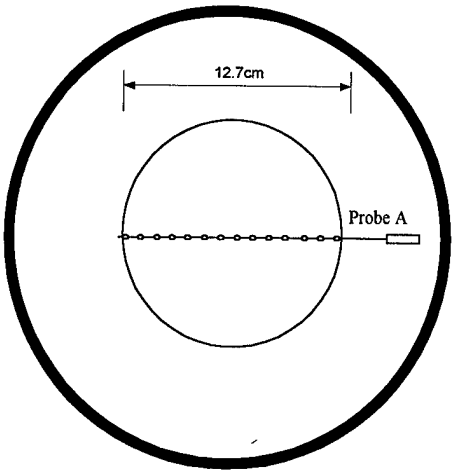


Figure 6. The top figure shows a sagittal cut and the figure below is a coronal cut through the applicator-phantom setup. The top schematic drawing shows the breast mimicking phantom submerged in the ultrasound transducer cylinder. The cylinder is filled with degassed coupling water. Below, the heavy circle indicates the transducer array, where all transducers are engaged, and the thin circle indicates the breast phantom outline. This probe configuration is one of several used for whole breast exposure experiment. The probe marked A was implanted in a position of the phantom, where the diameter is 12.7 cm.

As an example of our results, we will analyze four different sets of data shown in figures 7 - 14. Many different treatment geometries were measured, and the results below represent about 10 % of the total number of data sets.

Results and discussion:

Figure 7 shows a family of relative power deposition (SAR) profiles as measured by probe A. The rate of temperature rise was determined by monitoring the temperature at each sensor point during application of a power field. This experiment was subdivided into 3 power applications. In the first application (shown as filled diamonds), all the high frequency transducers were engaged to assess the ability to deposit power in the surface of the phantom in order to compensate for thermal conduction to the coupling water. It is clear from the "diamond" curve that most power is deposited at the surface of the breast phantom leaving less power deposition in the center (about 6 cm deep). In the second application (shown as filled squares), all the low frequency transducers were engaged to assess the ability to deposit power to the core of the phantom. This is also evident from the curve showing a power deposition peak in the center of the phantom at about 6 cm. In the third measurements (shown as filled triangles), all transducers were engaged at a ration of two parts power to the high frequency transducers and one part power to the low frequency transducers with the purpose of testing the ability to deposit power (SAR) both at the surface and at depth in the phantom. If this ratio of power deposition is retained for about 10 minutes, the thermal conduction will generate a relatively uniform temperature distribution reaching a quasi steady state condition. Figure 8 shows the temperature rise in the breast phantom resulting from the non-uniform power deposition (SAR) shown in Figure 7.

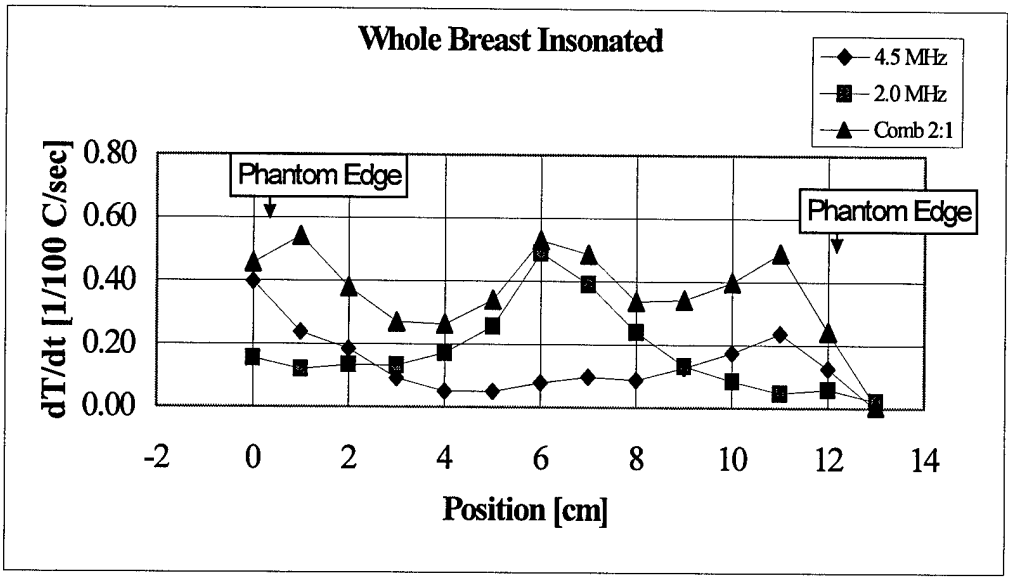


Figure 7. This figure shows a family of relative power deposition profiles measured by probe A in figure 6. This profile is measured through the center of the breast phantom at a position where the diameter of the phantom is 12.7 cm. The diamonds indicates the power being mostly deposited at the surface (edge) of the phantom due to the 4.5 MHz high frequency, the squares indicate that the 2.0 MHz low frequency mostly deposits power at the core of the phantom, and the triangles shows the ability to combine the low and high frequencies in order to achieve a more uniform power deposition profile.

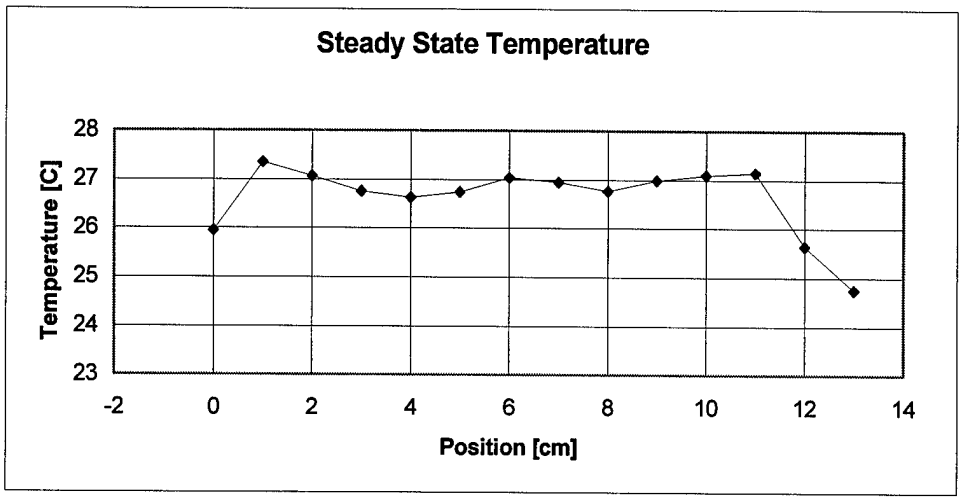


Figure 8. This figure shows the steady state temperature profile achieved during the experiment in shown in figure 7. Initially power (SAR) was delivered to both the low and high frequency transducers. After the temperature had increased by 4^{O}C at the center of the phantom, the low frequency transducers were decreased and controlled for maximum uniformity of the temperature profile.

Figure 8 demonstrates that the system is capable of delivering uniform temperature distribution to within +/- 0.5 ^{o}C in this plane throughout the breast phantom.

Figures 9 and 10 show the results of from insonating half the breast phantom. Figure 9 shows two cuts through the phantom setup as in figure 6. On the right, this figure indicates that temperature sensors in probe B are distributed differently than the sensors in probe A (figure 6) in that it has the temperature sensors concentrated in the left part of the phantom where the power deposition is expected. The heavy semi-circle indicated the part of the transducer array that is engaged for this experiment.

Figure 10 shows the resulting family of relative power deposition curves. Again, the high frequency transducers preferentially deposits power at the edge of the phantom (left part of diamond symbols), the low frequency transducers mostly at the center of the phantom (right part of square symbols). A combination of frequencies can be employed to deposit even amount of power at the surface and to the core of the phantom (circular symbols).

Figure 11 shows the phantom setup for insonating a quadrant of the breast. Temperature sensor B is utilized and the heavy quarter circle indicates which transducers that are engaged. Figure 12 shows the resulting power deposition profiles. The selective heating to the surface and the core of the phantom is now much less pronounced due to the fewer transducers and therefore lower geometrical gain of the setup. It is however still possible to selectively heat the surface or the core of the phantom.

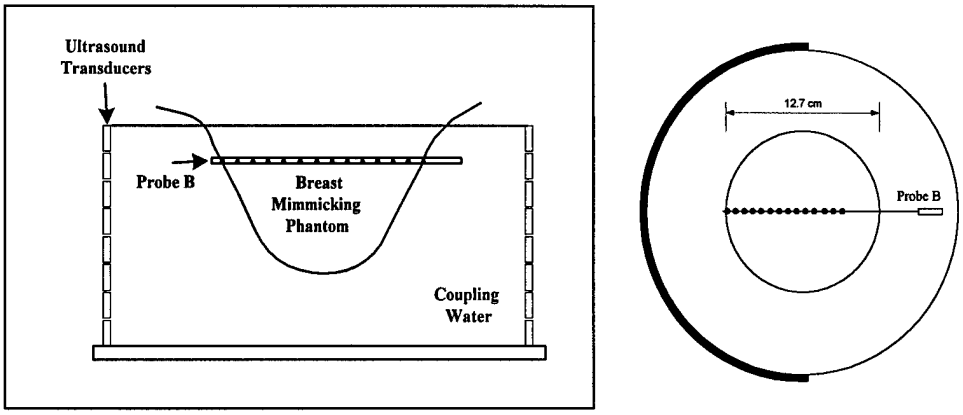


Figure 9 shows cuts through the applicator-phantom setup as in figure 6. The temperature probe shown on the right drawing is placed through the center of the phantom, with the sensors distributed through the left part of the phantom. The heavy semicircle on the right schematic drawing indicated that the left half of the transducer array is engaged.

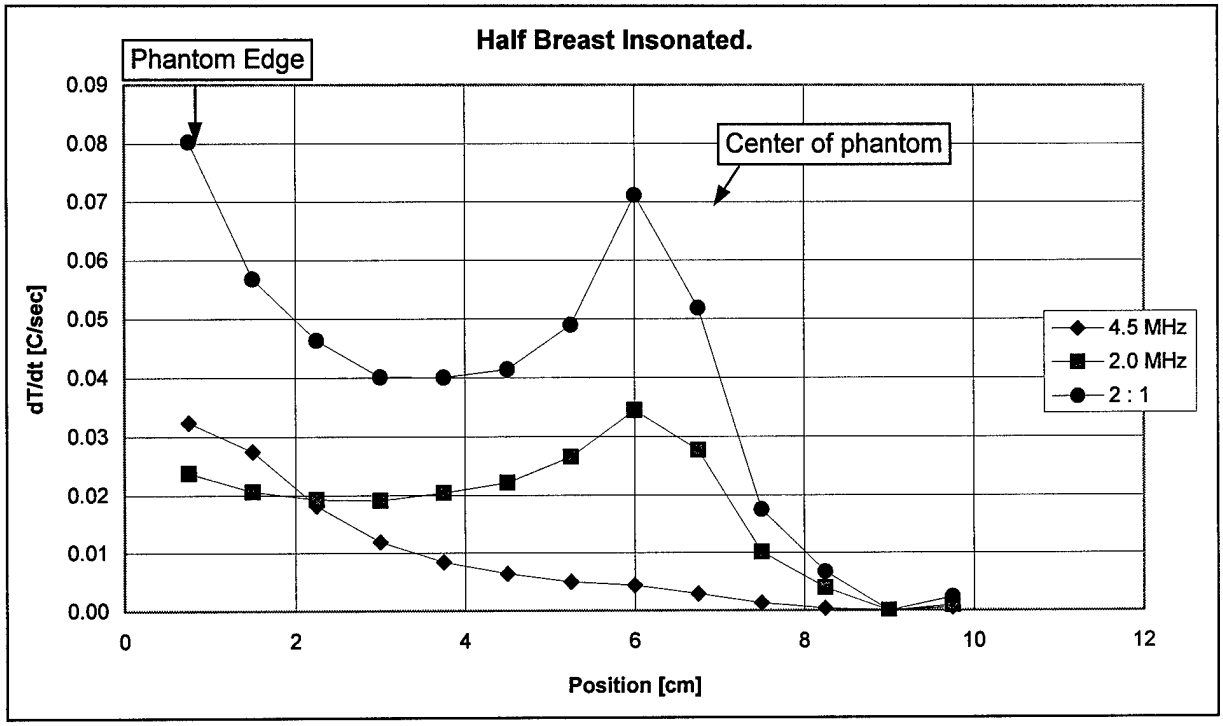


Figure 10. This figure shows a family of relative power deposition profiles measured by probe B in figure 9. This profile is measured through the center of the breast phantom at a position where the diameter of the phantom is 12.7 cm. The diamonds indicates the power being mostly deposited at the surface (edge) of the phantom due to the 4.5 MHz high frequency, the squares indicate that the 2.0 MHz low frequency mostly deposits power at the core of the phantom, and the circles shows the ability to combine the low and high frequencies in order to achieve a more uniform power deposition profile.

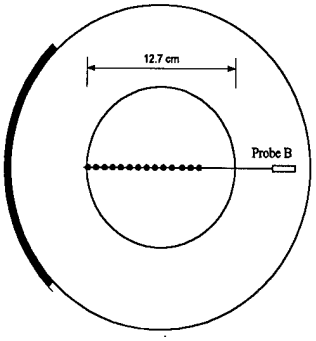


Figure 11. This figure shows a coronal cut of the experimental setup where one quadrant of the ultrasound transducers is engaged. Temperature probe B is placed as in figure 9, and the quadrant of transducers engaged is highlighted on the left of the schematic.

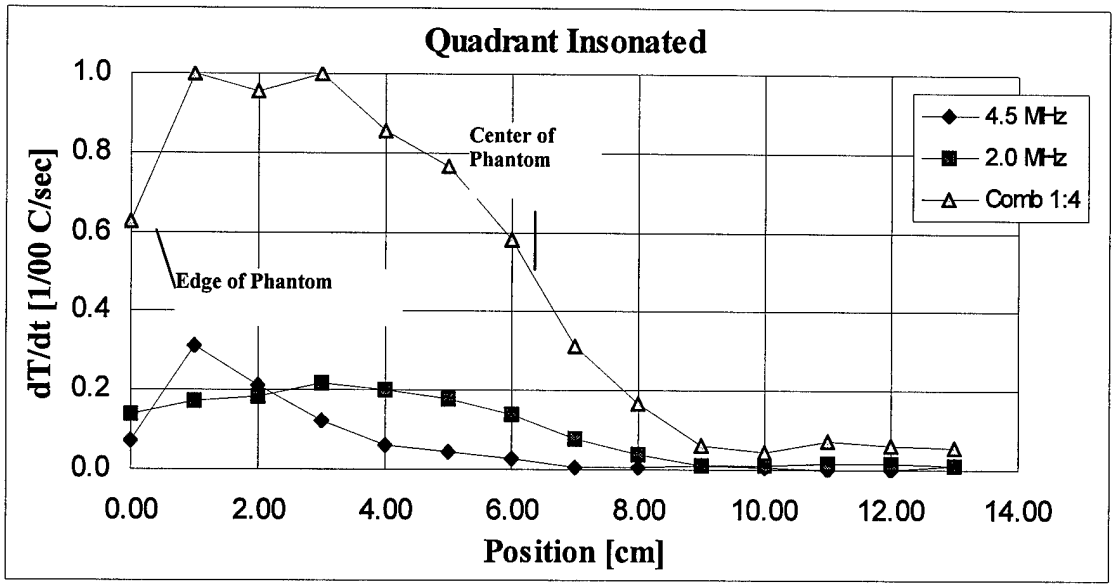


Figure 12 shows the relative power deposition profiles through the center of the irradiated quadrant of the breast. The diamonds indicate the power deposition profile when the high frequency transducers are engaged. The squares shows the same properties for the low frequency transducers, and the triangles shows the power deposition pattern when the transducers are engaged with a power a ration of 1:4 high to low frequency.

An experiment was performed to assess the deposition of power along the central axis of the breast phantom. Figure 13 shows the position of temperature probe C for this experiment. Figure 14 shows the resulting relative power deposition profile. The sensors at the apex (or tip) of the breast phantom is to the left, and the base of the phantom is to the right. As expected, the power deposition on the central axis close to the apex is highest due to a smaller diameter of the phantom at this position. This can easily be compensated by increasing the power to the rings closer to the base of the phantom.

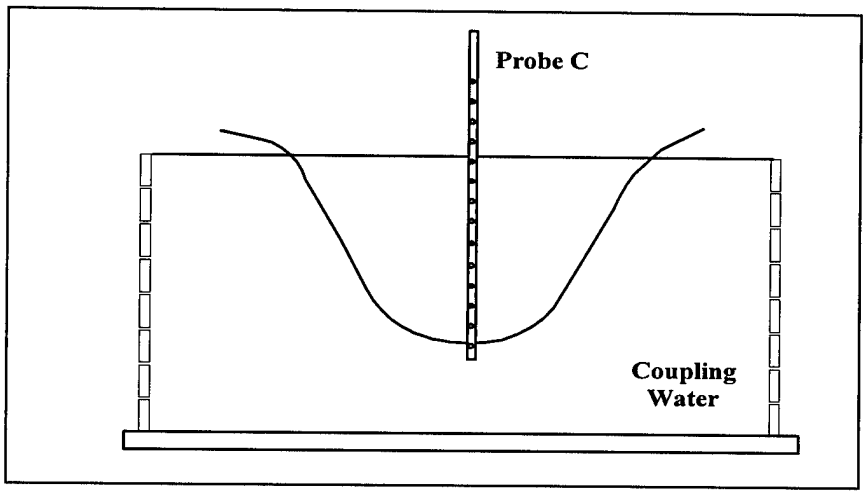


Figure 13. This figure shows the position of temperature probe C placed to demonstrate the uniformity of relative power deposition (SAR) along the central axis of the breast phantom. In this experiment the phantom was insonated with uniform power applied to the upper 5 rings.

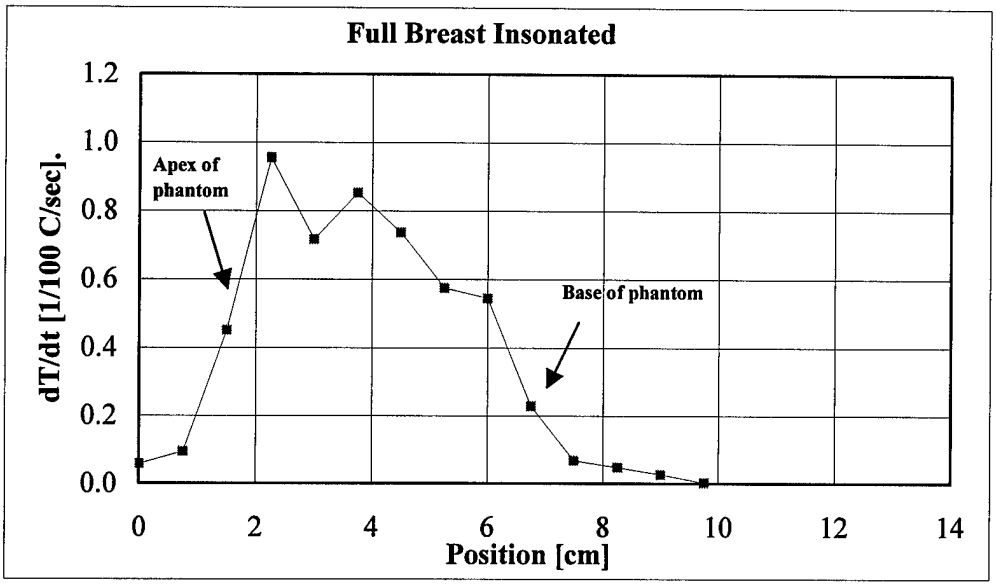


Figure 14. The relative power deposition profile resulting from supplying uniform power to all transducers in the upper 5 rings. The power delivered to each of the rings can be adjusted in order to achieve improved uniformity in the power deposition profile.

The temperature distributions have been measured in many coronal and sagittal planes in the breast phantom with the conclusion that the system has enough power output and control capability to achieve a uniform three dimensional temperature distribution throughout the breast phantom.

One characteristic of the breast treatment machine, is that the breast is submerged into a water bath during therapy, thus creating a water-soft tissue interface. The Ocheltree-Frizzell model used in our treatment planning efforts assumes a homogenous tissue medium, therefore creating errors in the calculated energy deposition at the water breast surface interface. A new complex theoretical model has been developed to correct for this interface problem (44).

D. Investigational Device Exemption (IDE) from the Food and Drug Administration (FDA), and Clinical Protocols.

The protocol that has been described in previous progress reports not been able to accrue any patients. We have decided to re-write the protocol with new inclusion criteria.

Initially, when this project was funded, the optimal treatment for patients with extensive ductal carcinoma in situ (DCIS) was not defined. Patients who exhibited extensive DCIS either with or without an invasive component experienced an increased rate of local failure after excision and standard external beam irradiation. It was felt that this would an ideal population in which breast hyperthermia would be of benefit. It was under these circumstances that the Hypothesis for this project was developed.

Since the development of the breast hyperthermia device there has been a growing consensus in the field that these women should undergo mastectomy. Although the goal of radiation is breast conservation, improvements in breast reconstruction, especially the advent of immediate reconstruction with a TRAM flap has increased the use of mastectomy in these situations. This is contrary to our original assumptions. After lengthy discussions with our radiation, surgical and medical oncology colleagues, we plan to resubmit this protocol for a slightly different patient population. Specifically, patients with focally positive or close surgical margins after excision for DCIS or invasive cancer will be eligible for hyperthermia treatment using the breast hyperthermia device.

The US Army Human Use Review and Regulatory Affairs Division require an institutional IDE before approving a new protocol and before granting permission to proceed with the clinical trial. The process of receiving an IDE and approval of protocols by the hospitals and the Army, is a lengthy process, which will take approximately nine months. Ten patients accrual for the initial device evaluation study may take another five to six months, altogether 15 months before the first phase of this study can be completed. The remaining funds for the current clinical study is insufficient to support this renewed effort, and a new No-cost extension for such a long time is not likely to be approved. Therefore we have decided to proceed with the new protocol and seek additional funding for the hyperthermia treatment of breast cancer using the completed breast therapy system.

VI. Conclusion and importance:

This final report demonstrates that the technical component of the Contract DAMD17-93-C3098 has been completed. A site-specific hyperthermia breast treatment system (BTS) has been built and accepted for clinical use. The system is capable of delivering hyperthermia as an adjuvant modality to the whole breast volume, and to a portion of the breast, which can be as small as a quadrant of the breast.

During the design, building and testing of the system, we experienced difficult technical, scientific, and regulatory challenges requiring complex solutions before the system could be completed and accepted. This has resulted in delays in the program and we were approved for two No-Cost extensions, the last one expiring on August 31st, 1999.

The importance of this work has been an attempt to address two of the goals suggested by the 1993 Institute of Medicine Report that was used by the USAMRMC to formulate its Broad Agency Announcements (BAA).

One of the goals was to identify new biologically based therapies to move away from todays relatively toxic treatments, and to offer more precise intervention that can eradicate the cancer, perhaps at its earliest stage, to improve local control, conserve the breast and reduce toxicity. The rationale for choosing adjuvant hyperthermia treatment of early stage breast cancer (DCIS and EIC) is based on the hypoxic environment in the target region that causes tumor cells to be less sensitive to the killing effects of radiation and more sensitive to the killing effects of hyperthermia. Therefore, hyperthermia has the potential of increasing local control without adding toxicity and may eliminate in many cases the need for disfiguring mastectomy. Unfortunately, this goal has not been achieved because today the best standard of treatment for this disease is in fact mastectomy. Therefore, as written, the DCIS protocol has not been able to accrue any patients.

The second goal relates to the mission of the Joint Center for Radiation Therapy (JCRT) to reach out beyond its academic headquarters at Harvard Medical School and provide cancer management in community hospitals that were previously under serviced. One objective of the USAMRMC breast research program is to support efforts to disseminate novel treatment approaches to women who are older, less affluent and more diverse than those women who normally enroll in academically based trials. We intend to make the hyperthermia treatment facility a regional resource that will include at least five community hospitals in a more ethnically diverse environment outside of Boston. Hyperthermia is particularly suitable for a regional approach, since only two treatment visits are needed for each patient. This goal is achieved, since the JCRT has a regional hyperthermia clinic, including microwave for chestwall treatments, ultrasound transrectal probes for prostate treatments, and the breast hyperthermia system available for treatments of intact breast pending approval of new protocols.

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IX. Personnel contributing to this effort:

Name, Title	Role in Program	Received support
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Irving Kaplan, M.D.	Clinical Investigator from June 1, 1998 to August 31, 1999	no
James Pelegatti, M.S.	Programmer	yes
Aliki Collins, Ph. D.	Post doctoral fellow to June 1994.	Yes
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Tami Hart, RTT	Radiation Therapist	Yes
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Stephen A. Goss, Ph.D.	Co-Investigator (subcontract)	Yes
M. Todd van Gundy, M.S.	R&D Engineer	Yes

Paul L. Neubauer	Associate Engineer	Yes
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Daniel Kapp, Ph.D., M.D.	Consultant, one annual review	Yes
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Terence Wong, Ph.D., M.D.	Consultant as needed	No
Rene Gonin, Ph.D.	Biostatistician, 10 days per year	yes